

REMARKS

Claims 1-19 are currently pending. Claims 2, 8, 14, 16, and 19 stand rejected under 35 U.S.C. § 112, first paragraph. Claims 1-19 stand rejected under 35 U.S.C. § 103(a) as being obvious in light of various references. Claims 1, 2, 8, 14-16, and 19 are amended herein and the amendments are supported by the Specification.

35 U.S.C. § 112, First Paragraph, Rejections

Claims 2, 8, 14, 16, and 19 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter which was not described in the Specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicant respectfully traverses the rejections.

Claims 2, 8, 14, 16 and 19 are amended herein. The amendments to the Claims overcome the outstanding rejection under 35 U.S.C. § 112, first paragraph, and are supported by the Specification, for example at paragraph [00010]. Applicant respectfully requests the withdrawal of the 35 U.S.C. § 112, first paragraph, rejection of amended Claims 2, 8, 14, 16, and 19.

35 U.S.C. § 103(a) Rejections

Claims 1-19 stand rejected under 35 U.S.C. § 103(a) as being obvious and unpatentable in light of the combination of Raijmakers et al. (U.S. Pat. No. 5,998,639), Simoons (U.S. Pat. No. 4,154,820), Raveendranath et al. (U.S. Pat. No. 5,288,717), Shah et al. (U.S. Pat. No. 6,525,039), Bender et al. (U.S. Pat. No. 5,998,638), and Kong et al. (U.S. Pat. No. 6,458,778). Applicant respectfully traverses the rejection.

In order to maintain a *prima facie* obviousness rejection certain criteria must be met. In particular:

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure.

See, M.P.E.P. §2142, citing In re Vaeck, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

The combination of references fails to meet these requirements with respect to Claims 1-19.

Therefore, Claims 1-19 are allowable over the 35 U.S.C. § 103(a) rejections.

Raijmakers et al. proposes a “method of production of sulfated steroid mixtures containing delta(8,9)DHE through sulfatation of an estrogen mixture containing delta(8,9)DHE or derivatives thereof which can be obtained by isomerization of equilin or a derivative thereof.” *See, Raijmakers et al.* at col. 2, lines 14-19. Raijmakers et al. does not propose the sulfation of alkali metal salts of estrogens.

Simoons proposes the use of tris (2-amino-2-hydroxymethyl-1,3-propanediol) as a stabilizer for use in making synthetic conjugated estrogen tablets. *See, Simoons* at col. 7, lines 15-40.

Raveendranath et al. proposes “alkali metal salts of 8,9-dehydroestrone sulfate ester free from other conjugated esters present in material found in natural sources of mixed esters.” *See, Raveendranath et al.* at col. 1, lines 36-40. Furthermore, the process proposed by Raveendranath et al. “relies upon the initial production of an alkali metal salt of 8,9-dehydroestrone followed by sulfation with trimethylaminesulfurtrioxide under mild conditions in a polar, aprotic solvent such as tetrahydrofuran with simultaneous or subsequent addition of tris(hydroxymethyl)aminomethane as a stabilizer.” *See, Id.* at col. 1, lines 53-59. Raveendranath et al. does not propose the sulfation of multiple alkali metal salts of other estrogenic compounds.

Shah et al., Bender et al., and Kong et al. propose the use of trimethylamine-sulfur trioxide complexes and/or triethylamine-sulfur trioxide complexes for the formation of estradienes, progestational agents, and estrogens.

The Action alleges that “the sulfatation of estrogen mixture would have been obvious to the skilled artisan at the time of the invention because (a) sulfatation of alcohols such as sterols utilizing a sulfur trioxide complex is well known in the art... (b) addition of a stabilizer such as Tris to estrogenic compositions is also well known... and (c) the level of skill of the ordinary artisan in the art at the time of the invention.” *See, Action* at p. 4. However, the references, even if combined, fail to teach or suggest all of the recitations of the claims and therefore fail to support a *prima facie* obviousness rejection.

Independent Claim 1 is amended herein and recites “reacting a sulfur trioxide complex with a mixture of at least two alkali metal salts of estrogens to provide a mixture of sulfated alkali metal salts of estrogens,” wherein the alkali metal salts of estrogens are alkali

metal salts of estrogens selected from the group consisting of “ $\Delta^{8,9}$ -dehydroestrone, estrone, equilin, 17 α -estradiol, 17 β -estradiol, 17 α -dihydroequilin, 17 β -dihydroequilin, equilenin, 17 α -dihydroequilenin, 17 β -dihydroequilenin, 17 α - $\Delta^{8,9}$ -dehydroestradiol, 17 β - $\Delta^{8,9}$ -dehydroestradiol, 6-OH equilenin, 6-OH 17 α -dihydroequilenin, 6-OH 17 β -dihydroequilenin, ethinyl estradiol, and estradiol valerate.” None of the references, alone or in combination, recite the reaction of a sulfur trioxide complex with a mixture of at least two alkali metal salts, particularly where the salts are selected from the group recited in Claim 1.

Raijmakers et al. may propose the sulfatation of an estrogen mixture containing delta(8,9)DHE or derivatives thereof but Raijmakers et al. does not propose sulfatation of alkali metal salts accomplished by “reacting a sulfur trioxide complex with a mixture of at least two alkali metal salts of estrogens to provide a mixture of sulfated alkali metal salts of estrogens” as recited in Claim 1. Although Raveendranath et al. may propose the production of an alkali metal salt of 8,9-dehydroestrone and its sulfatation with trimethylaminesulfurtrioxide in a polar, aprotic solvent, Raveendranath et al. does not propose the sulfatation of at least two alkali metal salts of estrogens as recited in Claim 1. Furthermore, Raveendranath et al. does not suggest or otherwise propose that the sulfatation of at least two alkali metal salts of estrogens to arrive at a mixture of sulfated estrogens would be desirable. The other references cited by the Action also fail to propose “reacting a sulfur trioxide complex with a mixture of at least two alkali metal salts of estrogens to provide a mixture of sulfated alkali metal salts of estrogens” as recited in Claim 1.

The failure of the references, either alone or in combination, to teach or suggest “reacting a sulfur trioxide complex with a mixture of at least two alkali metal salts of estrogens to provide a mixture of sulfated alkali metal salts of estrogens” as recited in Claim 1 precludes a *prima facie* obviousness rejection because each and every recitation of Claim 1 is not taught or suggested by the combination of references. *See, In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). Claim 1 is therefore allowable over the 35 U.S.C. § 103(a) obviousness rejection based on the combination of references.

Claims 2-14 depend from Claim 1 and are not obvious under 35 U.S.C. § 103(a) because the independent claim from which they depend is nonobvious. *See, In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988)(stating that if an independent claim is nonobvious under 35 U.S.C. § 103 then any claim depending therefrom is nonobvious); *see also*, M.P.E.P. § 2143.03. Claims 2-14 are allowable over the 35 U.S.C. § 103(a) rejection as dependent claims of a nonobvious independent claim.

Independent Claim 15 is amended herein and recites “reacting a mixture of at least two estrogens with sodium hydride in an apolar, aprotic solvent to provide a mixture of alkali metal salts of the estrogens” and “reacting sulfur trioxide-trimethylamine with the mixture of alkali salts of estrogens.” The cited references do not teach or suggest all of the recitations of Claim 15. As with Claim 1, the cited references do not teach or suggest the reaction of a mixture of alkali salts of estrogens with sulfur trioxide-trimethylamine to provide sulfated alkali metal salts of the estrogen mixture. The failure of the references to teach or suggest all of the recitations of independent Claim 15 precludes a *prima facie* obviousness rejection of Claims 15 under 35 U.S.C. § 103(a). *See, In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

Claims 16-19 depend from Claim 15 and as dependent claims are nonobvious because independent Claim 15 is nonobvious. *See, In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988)(stating that if an independent claim is nonobvious under 35 U.S.C. § 103 then any claim depending therefrom is nonobvious); *see also*, M.P.E.P. § 2143.03. Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejection of Claims 15-19.

Claims 1-19 are also allowable over the 35 U.S.C. § 103(a) obviousness rejections because there is no motivation to combine the references to arrive at the recitations of Claims 1-19. The Action alleges that the motivation for combining the references “is based on the knowledge in the art that compositions comprising a mixture of estrogenic sulfate esters are useful in hormone replacement therapy.” *See, Action* at p. 5. However, the knowledge that compositions comprising a mixture of estrogenic sulfate esters are useful in hormone replacement therapy does not motivate a combination of the references to arrive at the production of estrogenic sulfate esters using the processes of Claims 1-19. At most, the cited motivation would lead one of skill in the art to create mixtures of estrogenic sulfate esters. The combination of the references is not motivated.

None of the references teach the sulfatation of a mixture of “at least two alkali metal salts of estrogens” as recited in independent Claim 1. Furthermore, none of the references suggest “reacting a mixture of at least two estrogens with sodium hydride in an apolar, aprotic solvent to provide a mixture of alkali metal salts of the estrogens” and “reacting sulfur trioxide-trimethylamine with the mixture of alkali salts of estrogens” as recited in independent Claim 15. The alleged motivation may encourage the formation of mixtures of estrogenic sulfate esters but it does not encourage the formation of such mixtures according to the processes of Claims 1 and 15 because none of the references teach or suggest such

processes. At most, the alleged motivation may encourage a mixing of the final products of each of the references to form a mixture of estrogenic sulfate esters. A motivation to produce a particular product does not motivate or make obvious a process for arriving at that product, especially where none of the cited references teach or suggest all of the recitations of the process. The only reference that suggests the processes that may be combined with the alleged motivation to arrive at the processes of Claims 1 and 15 is the Specification, which cannot be used to motivate an obviousness rejection.

The lack of motivation to combine the references to arrive at the particular processes recited in independent Claims 1 and 15 precludes a *prima facie* obviousness rejection. *See, In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). Furthermore, as dependent claims of Claims 1 and 15, Claims 2-14 and 16-19 are also nonobvious because the independent claims from which they depend are nonobvious. *See, In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988)(stating that if an independent claim is nonobvious under 35 U.S.C. § 103 then any claim depending therefrom is nonobvious); *see also*, M.P.E.P. § 2143.03. Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) obviousness rejection of Claims 1-19 because no motivation exists to support a *prima facie* obviousness rejection of those claims.

CONCLUSION

The concerns of the Examiner addressed in full, Applicants respectfully request withdrawal of the outstanding rejections and the issuance of a Notice of Allowance forthwith. The Examiner is encouraged to direct any questions regarding the foregoing to the undersigned, who may be reached at (919) 854-1400.

Respectfully submitted,



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